IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Vonwiller, et al.
Appl. No.	:	10/552,881
Filed	:	16 April 2004
For	:	CROSS-LINKED POLYSACCHARIDE COMPOSITION
Examiner	:	Palenik, Jeffrey T
Group Art Unit	:	1615

DECLARATION UNDER 37 CFR §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Dr Geoffrey Kenneth Heber, declare and state:

1. I am a named inventor of the above-referenced patent application (***the Application***). I am also the Managing Director of Ultraceuticals R&D, Pty Ltd (***Ultraceuticals***), the assignee of the Application.

2. I am a cosmetic physician and am an expert in the field of cosmetic medicine, including the use of injectable dermal fillers. A copy of my Resume is annexed (**Exhibit A**).

3. I am a designated inventor on 18 patents or pending patent applications, I have authored two peer reviewed scientific papers in the field of cosmetic medicine, and have presented at twelve scientific meetings.

4. My research currently relates to the development and use of polysaccharide formulations for the treatment of conditions of skin.

5. I am familiar with the Application and the pending claims. I understand that the claims were rejected as being anticipated by Zhao et al (WO 00/46253), and obvious in light of Zhao in view of Malson et al. (WO 87/07898). I have reviewed the pending claims and these references, and herein describe additional experimental data supporting the unexpected and advantageous results obtained using the claimed process.

6. Ultraceuticals has developed cross-linked polysaccharide gel compositions made according to the process claimed in the Application. These gel compositions, which have a single type of cross-linkage, possess particular advantageous properties, including being substantially resistant to degradation (eg, enzymatic degradation), and are superior to the current market leading gels, Juvederm™ and Restylane™.

7. The advantageous properties of the gels are demonstrated by the Examples provided in the Application. Example 1 on page 10 of the Application demonstrates that the inventive process results in cross-linked polysaccharide gels having a single type of cross-linkage. The comparative data on pages 13-16, in particular Table 3 on page 16, shows that the cross-linked polysaccharide gels produced according to the process of the instant invention are more resistant to degradation than commercial gels (eg, Restylane™ and Perlane™).

8. As further evidence of the improved properties of the Ultraceuticals gel compositions prepared by the process claimed in the Application, I authorized and oversaw further comparative experiments comparing the Ultraceuticals gels with the current global market-leading gels, Juvederm™ and Restylane™.

9. Hyaluronic acid (*HA*) gels were prepared according to the process described and claimed in the Application, then analysed at three different concentrations: 20 mg/mL, 32 mg/mL, and 40 mg/mL. A typical analysis protocol is described below.

10. A 50 g batch of HA gel (cure time 30 minutes or 60 minutes) was dried for 6-8 hours under a dry nitrogen stream at 20 °C. The sample was weighed to determine HA weight and made up to the appropriate concentration (20 mg/mL, 32 mg/mL or 40 mg/mL) for milling 2-3 times at 212 microns. The gel was then sterilized at 121°C. Samples were made up to tare with sterile deionised water, mixed centrifuged and allowed to equilibrate overnight.

11. Hyaluronidase assays were performed on twin samples of 2 mg HA (dry weight) which were placed into eppendorf tubes, made up to 350 mg with phosphate buffered saline (***PBS***, pH 7.0), then the mixture was vortexed at an even suspension. PBS (50 µL) was added to one sample and enzyme was added to the other sample (50 µL PBS containing 0.1 mg/mL hyalruonidase: Sigma H3884 bovine testes; Type IV-S, lyophilized powder, 1010 units/mg solid). Both samples were then vortexed. The samples were incubated at 37°C for 18 hours. The assay was stopped by the addition of 100 µl of potassium tetraborate solution (0.4 mol/L; pH 9.1). These samples were then divided into two and heat treated at 80°C for 20 minutes. Ehrlich's solution (1.2 mL) was immediately added to each sample, which were then heated at 37°C for 30 minutes. The samples were then centrifuged for 5 minutes to pellet non-digested material and the absorbance measured at 585 nm.

12. On a weight for weight basis the gels prepared according to the Ultraceuticals process (having a single type of cross-linkage) had similar rheology to the Juvederm™ and Restylane™ gels and were suitable to flow through a fine gauge needle as recommended by the manufacturers of the Juvederm™ or Restylane™ gels.

13. The results of the comparative assays shown in the annexed figures (**Exhibit B** and **Exhibit C**) demonstrate that the Ultraceuticals gels had greater resistance to hyaluronidase than either of the current global market-leading gel products. Furthermore, on a weight for weight basis the Ultraceuticals gels had similar or less background soluble HA, which dissolves upon injection and does not contribute to a tissue augmentation effect.

14. The advantageous property of increased resistance to degradation (which was even better than the current market-leading products) was a significant and surprising result.

15. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

By: _____ Date: 21 September 2009

Dr Geoffrey Kenneth Heber

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Exhibit A

RESUME OF GEOFFREY KENNETH HEBER

1980: MBBS (Hons), University of New South Wales.

1985: Diploma of Obstetrics, Royal Australian College of Obstetricians and Gynaecologists.

1990: MBA, University of Sydney.

2001-2009: Fellow of the Faculty of Medicine, Australasian College of Cosmetic Surgery.

2001-2009: Member, Cosmetic Physicians Society of Australia.

2001-2002: Member, NSW Cosmetic Surgery Credentialing Committee, a NSW Government convened/funded body administered by the Australian Medical Association.

1988-2009: Partner, Heber Davis Skin Clinic (www.heberdavis.com.au), a medical practice specialized solely in non-surgical cosmetic medicine, including cosmetic injectable, laser and light based therapies.

1991-2001: Founder and Executive Chairman, Doctors Formula Pty Ltd, an importer of skincare products sold through department stores, doctors and beauty therapists.

2001-2009: Founder and an Executive Chairman, Ultraceuticals Pty Ltd, a manufacturer of skincare products sold through department stores, doctors and beauty therapists.

2001-2009: Founder and Executive Chairman, Ultraceuticals R&D Pty Ltd, a company formed to research and develop dermal filler technologies.

Refereed Publications and Conference Presentations

- Heber, G. K., Hayes, A. J. and Markovic, B. (2006) An Immunohistological study of anhydrous topical ascorbic acid compositions on *ex vivo* human skin, *Journal of Cosmetic Dermatology*, 5: 150–156.

- Heber, G. K. (2005). Low frequency sonophoresis of retinol and L-ascorbic acid for photoageing: A controlled prospective pilot study, *Australasian Journal of Cosmetic Surgery*, 1: 42-49.

- Heber, G. K. (2009). Retinol and Tretinoin for Photoageing: A Pilot Study, Presentation at *Annual Scientific Meeting of Australasian College of Cosmetic Surgery*, Darling Harbour, Sydney.

- Heber, G. K. (2006). An in Vitro Study of Anhydrous Topical Ascorbic Acid Compositions on *Ex Vivo* Human Skin, 5th World Congress of the International Academy of Cosmetic Dermatology, Melbourne

- Heber, G. K. (2005). An *in vitro* study of a novel non-aqueous L-ascorbic acid topical formulation, Presentation at Annual Scientific Meeting of Chinese Dermatological Society of Taiwan, Taipei, Taiwan.

- Heber, G. K. (2005). Techniques & ingredients for improvement in stubborn skin conditions, Skin Sciences and Aesthetic Therapies Symposium, 39th *Annual Conference of the Australasian Society of Cosmetic Chemists*, Brisbane, Queensland.

- Heber, G. K. (2004). Cosmeceuticals for physicians, Presentation at *Annual Scientific Meeting of Appearance Medicine Society of Australasia*, Wellington, New Zealand.

- Heber, G. K., (2004). Hyperpigmentation, Presentation at *Annual Scientific Meeting of Appearance Medicine Society of Australasia*, Wellington, New Zealand.

- Heber, G. K., (2004). Peels, Presentation at *Annual Scientific Meeting of Appearance Medicine Society of Australasia*, Wellington, New Zealand.

- Heber, G. K. (2004). An *in vitro* study of a novel non-aqueous L-ascorbic acid topical formulation, Presentation at *Annual Scientific Meeting of Australasian College of Cosmetic Surgery*, Canberra, ACT.

- Heber, G. K. (2003). Skin ageing, Presentation at *Annual Scientific* Meeting of *Appearance Medicine Society of Australasia*, Auckland, New Zealand.

- Heber, G. K. (2003). Dermal fillers, Presentation at *Annual Scientific Meeting of Appearance Medicine Society of Australasia*, Auckland, New Zealand.

- Heber, G. K. (2003). Topical treatment of skin ageing, Presentation at *Annual Scientific Meeting of Australasian College of Cosmetic Surgery*, Gold Coast, Queensland.

- Heber, G. K. (2002). Particle free microdermabrasion, *Presentation at Annual Scientific Meeting of Australasian College of Cosmetic Surgery*, Sydney.

Ultraceuticals memberships and development grants

- Member organization NSW Government Australian Technology Showcase administered by NSW Department of State and Regional Development for "vitamin C technology" (2004-2007).
- Biobusiness Grants: NSW Department of State and Regional Development: Development of hyaluronic acid gels, $14,350 (2006); Development of manufacturing specifications of hyaluronic acid gels, $16,650 (2005); Study of effects of vitamin C and polysaccharides on human skin, $22,000 (2005); USA market development consultancy $19,412 (2004).
- Australian Government Export Market Development Grants: (2004:$119,000; 2005:$136,000; 2006:$130,000).

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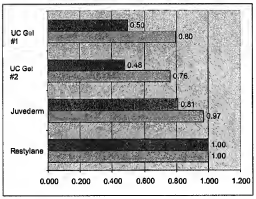
Exhibit B

Ultraceuticals Gels 32 mg/mL

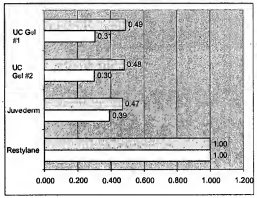
Greater Hyaluronidase Resistance



◆ Hyaluronidase degradation (as a % of Restylane 20mg/ml on a total weight basis)

◈ Hyaluronidase degradation (as a % of Restylane on a weight for weight basis)

Lower Background Soluble HA



◇ Background (as a % of Restylane on a total weight basis)

◈ Background (as a % of Restylane on a weight for weight basis)

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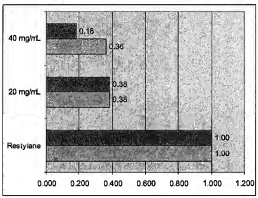
Exhibit C

Ultraceuticals Gels 20 mg/mL & 40 mg/mL

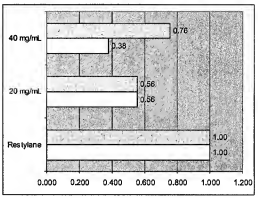
High Hyaluronidase Resistance



◆ Hyaluronidase degradation (as a % of Restylane on a total weight basis)

◈ Hyaluronidase degradation (as a % of Restylane on a weight for weight basis)

Low Soluble HA



◇ Background (as a % of Restylane on a total weight basis)

◇ Background (as a % of Restylane on a weight for weight basis)